MEMORANDUM

Re: SUGGESTIONS FOR ADDITIONAL RESEARCH
(An extension of conversation of September 27th, 1967, with Dr. Robert Carpenter)

1) Inhibitors of Carcinogenesis

In the course of our studies on co-carcinogens, we observed that orange oil (obtained from Magnus, Mabee & Reynard, Inc.) exerts a marked inhibition of dibenzpyrene (benzo[rst]pentaphene) carcinogenesis in our standardized system of subcutaneous injection in C57BL/6 mice. This inhibitory effect, which has not been previously described, is dose-dependent, as may be seen from the data in Figure 1. When given intravenously, orange oils reduced the increase of lung adenomas which followed intravenous injection of dibenzpyrene in A mice.

These orange oils have also been shown by Dr. J.Z. Gabliks of M.I.T. (now with Northeastern University) to be cytotoxic in cell culture systems.

Previously, orange oils had been described by Roe and Field of London, to possess co-carcinogenic effects in mouse skin and in the forestomach of mice having been pre-treated with topical application or ingestion, respectively, of benzpyrene (Roe, F.J.C. and Field, W.E.H., Chronic Toxicity of Essential Oils and Certain Other Products of Natural Origin, Food and Cosmetics Toxicology 3:311-323, 1965).

We believe that our surprising observation of dose-related anti-carcinogenic effect of crude orange oil justifies a study of the effects upon mouse skin of cigarette smoke condensates obtained from cigarettes containing orange oils or terpenes derived from orange oils.

Experiments of this nature could be designed to answer the question whether addition of certain terpenes (orange oils) to cigarettes would exert a co-carcinogenic, an anti-carcinogenic or an anti-co-carcinogenic effect upon the condensates resulting from such cigarettes.

The results of such studies are, of course, totally unpredictable. On the other hand, we believe that the equilibrium in cigarette tars between initiators, promoters and inhibitors of carcinogenesis is so labile that, whenever substances are found that possess inhibitory action, these ought to be studied. This is especially true when the substance that might be beneficial is a waste product of an agricultural commodity generally

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considered safe for human consumption (orange oil).

2) Acute Toxicity of Cigarette Smoke

It is a fundamental principle of toxicology that determination of acute toxicity serves as a basis for the study of toxic phenomena and provides the information necessary (in the case of consumer products) to establish safety of use. In general, an attempt is made to study acute toxicity of consumer items such as drugs, food additives, colors and preservatives by the route of administration corresponding to the proposed consumer's use.

These toxicological principles have largely been ignored in studies dealing with tobacco products. Most studies on acute effects of inhaled cigarette smoke have been done in humans and deal only with the vasoconstrictive effects of nicotine, or else acute toxicity has been determined in various species in vivo and in vitro only with regard to cilia and mucus.

Our studies on the systemic acute toxicity of fresh, inhaled mainstream smoke in mice have shown that cigarette smoke has lethal effects upon mice and that fresh mainstream smoke of cigarettes, at dilutions of 1:4 or less, leads to death in from 10 to 35 minutes, depending on the brand of cigarettes smoked. The length of survival is not always correlated with the nicotine or tar content of the cigarette. Prevention of nicotine toxicity by pretreatment with antinicotine compounds does not fully protect, suggesting that there are lethal factors in the gas phase. Such factors may be studied separately in Cambridge or Millipore-filtered smoke.

Some, but not all, of the toxicity of the gas phase is, of course, due to carbon monoxide. We believe that studies on the acute toxicity of cigarette mainstream smoke with appropriate chemical monitoring of the composition of the gas phase could serve as a guide for reduction of the acute toxicity of cigarette smoke.

While the role of tar in carcinogenesis is probably as important as that of other smoke components, the role of gas phase components as irritants (leading to emphysema) and as possible co-carcinogens (both through their cilia-toxic effect, facilitating deposition of larger amounts of tar, and by their direct chemical promoting effect) is probably more important than generally assumed.

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Reduction of the acute toxicity of cigarette mainstream smoke would suggest that such cigarettes are not only less toxic, but also less irritant and less co-carcinogenic.

It is also prudent to anticipate that, sooner or later, standards will be set by regulatory agencies and may include acute toxicity studies in the case of cigarettes, as they do in the case of many other regulated consumer products.

For these reasons, scientific and practical, we suggest that you consider a program toward the development and use of methods for the study of acute toxicity of cigarette smoke.

We are looking forward to a discussion of these matters on your next visit to Cambridge.

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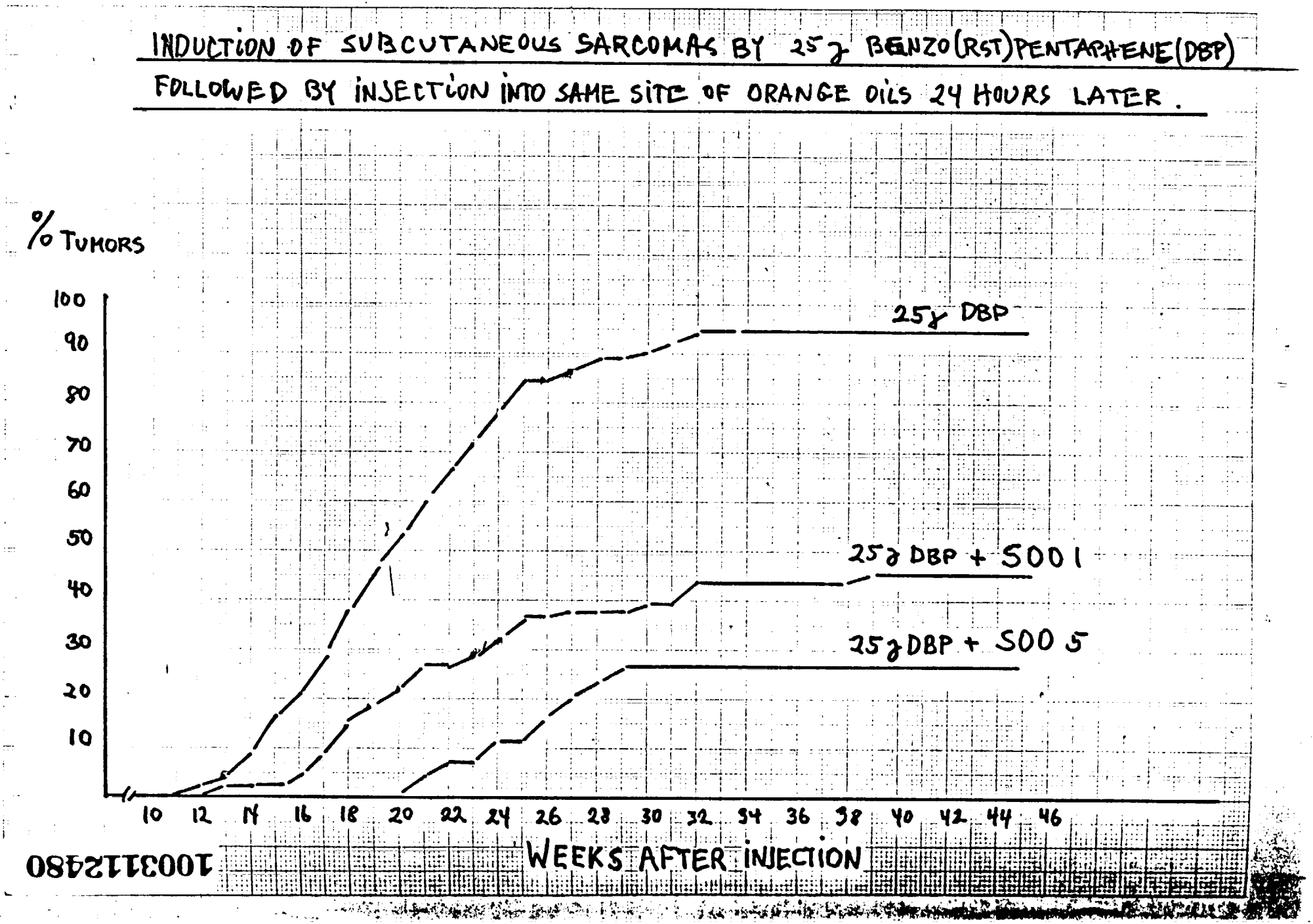
Source: https://www.industrydocuments.ucsf.edu/docs/lfyl0000

Figure 1



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